

APPLICATION OF THE HURD-MORI REACTION FOR THE SYNTHESIS OF CHIRAL 1,2,3-THIA(SELENO)DIAZOLE DERIVATIVES FROM (+)-3-CARENE AND α -PINENE

Morzherin Yu.Yu.,^a Glukhareva T.V.,^a Mokrushin V.S.,^a Tkachev A.V.,^b and Bakulev V.A.^a

^a The Urals State Technical University, 620002 Ekaterinburg, Russian Federation.
Fax: +7 3432 745483, e-mail: morjerine@htf.ustu.ru

^b Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences,
630090 Novosibirsk, Russian Federation, e-mail: atkachev@nioch.nsc.ru

Abstracts Chiral 1,2,3-thiadiazoles derivatives containing either cyclopropyl or cyclobutyl groups were synthesized from seco-derivatives of (+)-3-carene and α -pinene by the Hurd-Mori reaction.

Introduction

1,2,3-Thiadiazoles are known to be useful synthons in organic synthesis (4,5). Very active cotton defoliant and plant activator were found among them recently (1-3). In the course of our research work we were interested in functionalized chiral 1,2,3-thiadiazoles **1,2** as potential fungicides. To prepare 1,2,3-thiadiazoles **1,2** we used Hurd and Mori (6,7) reaction. Oxo nitriles **3,4** prepared from natural monoterpenes (+)-3-carene **5** and α -pinene **6** by known method (8) were taken of as starting reagents.

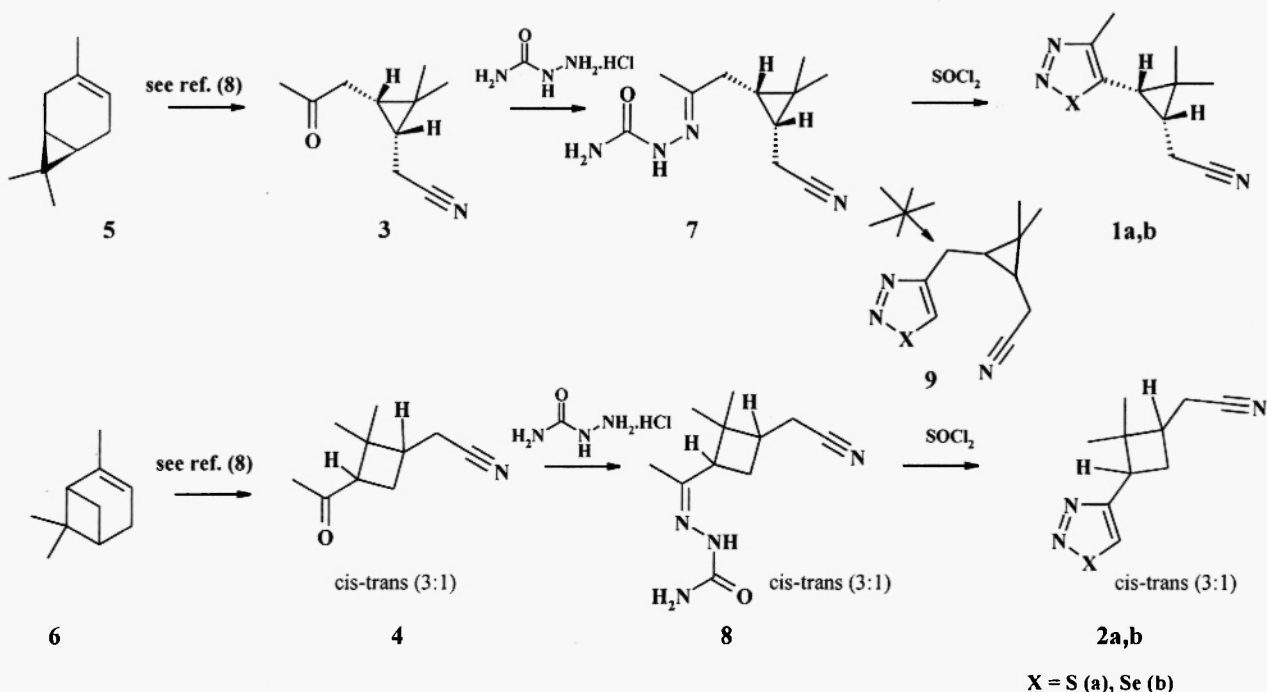
Results and Discussion

The semicarbazones **7, 8** were readily prepared from the corresponding oxo nitriles **3, 4** by reaction with semicarbazide hydrochloride at room temperature. When compounds **7, 8** were treated with thionyl chloride at room temperature in CH_2Cl_2 thiadiazoles **1a, 2a** were formed in 78 and 60% yields. Only the products of the destruction of the ring were found if this reaction was carried out at higher temperatures.

Generally, both methylene and methyl groups of the substituted acetone moiety in compound **7** could take part in the cyclization process to form isomeric products **1a** and **9**. Nevertheless, we have shown that the reaction of oxo nitrile **7** with thionyl chloride proceeds with high regioselectivity on the methylene group to form thiadiazole **1a** as the only product and isomeric 1,2,3-thiadiazole **9** is not detected. The formation of compound **1** is in agreement with a series of observations on reactivity of the substituted acetone moiety in compound **3**: most of reactions involve just the methylene group rather the methyl – intramolecular cyclization (9), C-nitrosation (10), bromination (11). When treated with SeO_2 in ethanol, semicarbazones **7** or **8** produce 1,2,3-selenodiazoles **1b** or **2b**. The 1,2,3-selenodiazoles are very unstable and are decomposed at 30-40°C or at room temperature in various solvents. Mass-spectra of the 1,2,3-selenadiazoles contain picks of the molecular ions having the ratio of isotope line characteristic for the compound with one selenium atom.

In contrast to optically active 3-carene derivative **3**, for the preparation of seco-pinane derivatives we used racemic oxo nitrile **4** as ca. 3:1 mixture of *cis*/*trans* isomers. Formation of the products **8** and **2** with the same isomeric ratio indicates that no epimerization occurs during the reaction and compounds **8** and **2** can be prepared in optically active form provided that the starting α -pinene is optically active.

Thus, we have demonstrated that a simple two-step syntheses of chiral 1,2,3-thiadiazoles **1a**, **2a** and 1,2,3-selenodiazoles **1b**, **2b** are readily achieved using available oxo nitriles **3**, **4** as the starting materials. All the reactions proceed under very mild conditions to give the final products in high yields.



Experimental

Unless other noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Dry CH_2Cl_2 was prepared by distillation over P_2O_5 . Analytical TLC plates were Silufol[®] (Silpearl on aluminium foil). Preparative column chromatography was performed on SiO_2 (0.140-0.315 mm, air dried and activated at 120°C for 4h) ^1H and ^{13}C NMR spectra were recorded in $[\text{}^2\text{H}_6]\text{DMSO}$ and CDCl_3 solutions on a Bruker DRX-500 (500 MHz for ^1H and 125 Hz for ^{13}C) and Bruker WH-250 (250 MHz for ^1H) using signals of the solvents as the internal standard (δ_{H} 2.55 ppm and δ_{C} 39.50 ppm for DMSO, δ_{H} 7.24 ppm and δ_{C} 76.90 ppm for CDCl_3). IR spectra (in KBr) were obtained using a UR-20 spectrometer. A Polamar A polarimeter was used to measure optical rotation at 578 nm at 30°C . Mass spectra were obtained on a Finnigan MAT 8200 instrument using the electron impact ionization technique ($40\text{--}200^\circ\text{C}$, 70 eV). New compounds **1a**, **2a**, **7**, **8** gave satisfactory element analyses $\pm 0.35\%$.

[(1*R*,3*S*)-2,2-Dimethyl-3-(2-oxopropyl)-cyclopropyl]-acetonitrile **3** and (3-acetyl-2,2-dimethylcyclobutyl)-acetonitrile **4** (ca. 3:1 mixture of *cis*- and *trans*- isomers) were prepared by known method (8) via nitrosochlorination of (+)-3-carene and α -pinene, respectively.

General procedure for the preparation of the simecarbazones

An oxo nitriles **3** or **4** were added to an aqueous solution of 1 equivalent of semicarbazide hydrochloride. The reaction mixture was stirred at room temperature for 4 hours. The crystalline product was collected and dried under vacuum to give compounds **7** or **8** in 93 and 75% yield, respectively. The products were pure enough for further reactions. An analytical samples were prepared by crystallization from 95% aq. ethanol.

(1*S*,3*R*)-1-(2,2-Dimethyl-3-cyanomethylcyclopropyl)acetone semicarbazone **7**: white powder, mp 182-184°C; NMR ¹H (DMSO-D₆, δ, ppm, J/Hz): 8.86 (1H, s, NH), 6.14 (2H, s, NH₂), 2.5 - 2.6 (2H, m, CHCH), 2.18 (2H, d, 6.6, CH₂), 1.80 (3H, s, Me), 1.05 (3H, s, Me), 0.96 (3H, s, Me), 0.83 (2H, d, 6.9, CH₂). MS, *m/z* (%): 223 (M⁺, 1.7). IR (KBr), ν/cm⁻¹: 3460, 3270, 3190 (N-H), 2960, 2940, 2860 (C-H), 2230 (C≡N), 1680 (C=O). Found, %: N 24.84. Calculated for C₁₁H₁₈N₄O, %: N 25.21.

1-(2,2-Dimethyl-3-cyanomethylcyclobutyl)-methylketone semicarbazone **8** (ca. 3:1 mixture of *cis*- and *trans*- isomers): white powder, mp 200-202°C; NMR ¹H (DMSO-D₆, δ, ppm, J/Hz): 8.86 (1H, s, NH), 6.17 (2H, s, NH₂), 1.6-2.2 (6H, m, CHCH₂CHCH₂), 1.59 (3H, s, Me), 1.22 (3H, s, Me), 0.77 (3H, s, Me). MS, *m/z* (%): 223 (M⁺, 2.7). IR (KBr), ν/cm⁻¹: 3160 (NH), 2960 (C-H), 2240 (C≡N), 1680 (C=O). Found, %: N 24.26. Calculated for C₁₁H₁₈N₄O, %: N 25.21.

General procedure for the preparation of the thiadiazoles

A suspension 0.5 g of **7** or **8** in dry dichloromethane (20 mL) was treated with 20 equivalents of SOCl₂ in one portion and stirred for 6 h at room temperature. Water (20 mL) was added, the organic phase was separated, dried with Na₂SO₄ and concentrated in vacuum. The oily residue was chromatographed on a silica gel column using hexane – ethyl acetate (1:2) as eluent to afford thiadiazoles **1a** or **2a**.

4-Methyl-5-[(1*S*,3*R*)-2,2-dimethyl-3-cyanomethylcyclopropyl]-1,2,3-thiadiazole **1a**: Yield 0.23 g (56%); oil. [α]_D²⁰ +4.94 (c 0.0162, CHCl₃). NMR ¹H (CCl₄ – acetone-d₆, 4:1 v/v, δH, ppm, J/Hz): 2.65 (3H, s, Me_{thiadiazole}), 2.34 (1H, dd, 17.5, 7.4, CHH), 2.20 (1H, dd, 17.5 and 8.0, CHH), 2.00 (1H, d, 8.8, CH), 1.58 (1H, ddd, 8.8, 8.0 and 7.4, CHCH₂), 1.38 (3H, s, Me), 1.15 (3H, s, Me). NMR ¹³C (CDCl₃, δ, ppm): 158.83 (C₍₅₎), 145.081 (C₍₄₎), 117.32 (CN), 27.94 (Me_{thiadiazole}), 25.49 (CH), 22.95 (CHCH₂), 22.00 (CMe₂), 15.85 (Me), 14.08 (CH₂), 12.67 (Me). IR (CCl₄), ν/cm⁻¹: 2940, 2900, 2840 (C-H), 2230 (C=N). UV (EtOH, λ nm, lg ε): 223 (3.66), 266 (3.64). MS, *m/z* (%): 208.09029 (M+1, 4.52). Calculated for C₁₀H₁₃N₃S+H. 208.090. Found, %: N 20.50; S 15.50. Calculated for C₁₀H₁₃N₃S, %: N 20.27; S 15.47.

4-(2,2-Dimethyl-3-cyanomethylcyclobutyl)-1,2,3-thiadiazole **2a** (ca. 3:1 mixture of *cis*- and *trans*- isomers): yield 0.28 g (60%); brown liquid. NMR ¹H (CDCl₃, δ, ppm): *cis*-isomer: 8.12 (1H, s, C₍₅₎H), 3.54 (1H, dd, J = 10.4 and 7.6 Hz, CH), 2.0-2.6 (5H, m, CH₂CHCH₂), 1.23 (3H, s, Me), 0.62 (3H, s, Me); *trans*-isomer: 8.16 (1H, s, C₍₅₎H), 3.63 (1H, dd, J = 9.1 and 6.2 Hz, CH), 2.0-2.6 (5H, m, CH₂CHCH₂), 1.18 (3H, s, Me), 0.65 (3H, s, Me). NMR ¹³C (CDCl₃, δ, ppm): *cis*-isomer: 162.4 (C₍₄₎), 131.5 (C₍₅₎), 118.3 (CN), 42.9 (CMe₂), 40.8 (CH), 38.1 (CHCH₂), 29.1 (Me), 27.4 (CH₂), 17.1 (CH₂CN), 17.0 (Me); *trans*-isomer: 163.3 (C₍₄₎), 131.5 (C₍₅₎), 118.7 (CN), 41.1 (CMe₂), 40.3 (CH), 37.9 (CHCH₂), 27.0 (CH₂), 24.6 (Me), 23.2 (Me), 17.9 (CH₂CN). IR (CCl₄), ν/cm⁻¹: 2950, 2910, 2850 (C-H), 2230 (C≡N). UV (EtOH, λ nm, lg ε): 212 (3.43), 261 (3.25). MS, *m/z* (%): 207.08544 (M⁺, 6.49). Calculated for C₁₀H₁₃N₃S 207.08301. Found, %: N 20.15; S 15.30. Calculated for C₁₀H₁₃N₃S, %: N 20.27; S 15.47.

General procedure for the preparation of the selenodiazoles.

A suspension 0.5 g of **7** or **8** in ethanol (20 mL) was treated with 20 equivalents of SeO₂ in one portion and stirred for 6 h at room temperature. After filtration the organic was concentrated in vacuum at room temperature. The oily residue was chromatographed on a silica gel column using hexane – ethyl acetate (1:2) as eluent to afford selenodiazoles **1b** or **2b**.

4-Methyl-5-[(1S,3R)-2,2-dimethyl-3-cyanomethylcyclopropyl]-1,2,3-selenodiazole 1b: yield 0.38 g (67%); brown liquid. NMR ¹H (CDCl₃, δ , ppm, J/Hz): 2.78 (3H, d, J=0.9, Me_{selenodiazole}), 2.44 (1H, dd, J=17.1 and 6.5, CHH), 2.42 (1H, dd, J=17.1 and 7.9, CHH), 2.20 (1H, d, J=9.7, CH), 1.67 (1H, ddd, J=6.5, 7.9 and 9.7, CH), 1.39 (3H, s, Me), 1.15 (3H, s, Me). MS, *m/z* (%): 214 (M–N₂–Me, 1.03), 212 (5.29), 210 (2.63), 209 (1.02), 208 (1.09), 189 (1.85), 188 (1.11), 187 (10.19), 186 (1.90), 185 (6.47), 184 (3.04), 183 (2.92), 182 (1.04).

4-(2,2-Dimethyl-3-cyanomethylcyclobutyl)-1,2,3-selenodiazole 2b (ca. 3:1 mixture of *cis*- and *trans*-isomers): yield 0.38 g (67%); brown liquid. NMR ¹H (CDCl₃, δ , ppm): 8.21 (1H, s, CH₍₅₎), 3.50–3.65 (1H, m, CH), 2.0–2.6 (5H, m, CH₂CHCH₂), 1.28 (3H, s, Me), 0.72 (3H, s, Me). MS, *m/z* (%): 227 (M–N₂, 3.87), 225 (2.02), 189 (12.61), 188 (1.35), 187 (6.93), 186 (2.88), 185 (4.53), 184 (1.25), 183 (1.59), 182 (1.32).

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